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Impact of sofosbuvir/ledipasvir versus sofosbuvir/daclatasvir regimens on the male sexual function of patients with chronic hepatitis C

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SUMMARY

Direct-acting antivirals (DAAs) are associated with remarkable efficiency and safety profiles; however, their effect on erectile function remains insufficiently studied. This study included 200 male patients with chronic hepatitis C virus (HCV) infection divided into groups A and B and 100 healthy controls. Group A received sofosbuvir (SOF) 400 mg/ledipasvir 90 mg (Harvoni), whereas group B received SOF 400 mg/daclatasvir 60 mg for 3 months. The Arabic version of the five-item International Index of Erectile Function-5 (IIEF-5) questionnaire was used to assess erectile function before and after completion of therapy and 3 months after. Erectile dysfunction (ED) was present in 74.5% of the patients and 14% of the controls. Immediately after treatment, group B (22.5±2.6) had a significantly higher mean IIEF-5 score than did group A (17.3±3.3) ($p<0.001$). Three months after treatment, all groups had no significant differences in mean IIEF-5 scores (group A: 23.1±1.9, group B: 23.3±1.9, controls: 23.7±2.3); however, free testosterone (FT) levels were significantly higher compared with pre-treatment. Both treatment regimens were associated with the improvement of erectile function and sex hormonal milieu. SOF/daclatasvir was associated with earlier improvement of erectile function compared with SOF/ledipasvir.

Keywords: HCV, DAA, ledipasvir; dacaltasvir; sofosbuvir.

INTRODUCTION

Hepatitis C virus (HCV) infection is an important public healthcare concern, with more than 170 million reported cases globally [1]. Egypt is known to have the highest HCV prevalence worldwide, with more than 14.7% of the Egyptian adults having been exposed to the virus [2]. Meanwhile, cirrhosis is considered the end result of an ongoing inflammatory and fibrotic process induced by HCV. Treatment regimens traditionally included several interferon (IFN)-based combinations. Later on, IFN-free regimens gained popularity by combining different classes of direct-acting antivirals (DAAs), which were associated with a greater sustained viral response and remarkable safety profiles [3, 4].

The discovery of DAAs is considered a breakthrough in the management of chronic HCV infection. These agents target several viral proteins, such as NS3/4A protease and NS5B polymerase. Sofosbuvir (SOF) is currently considered a mainstay in the treatment of HCV genotype 4, the genotype with the highest prevalence in Egypt. It is also considered a pangenotypic agent in combination with other DAAs. When combined with ledipasvir (SOF/LDP), it interferes with HCV replication by inhibiting the HCV nonstructural proteins NS5A and NS5B. On the other hand, da-

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clatasvir inhibits the HCV nonstructural protein NS5A [5, 6]. Among patients treated with interferon-free DAA regimens, it was reported that about 96.8% achieved sustained viral response (SVR) and 3.2% were no SVR. High sustained viral response (SVR) rates 95.1% with SOF + DAC and 99% with SOF/LDP were reported among Egyptian patients [8, 9].

Sexual dysfunction is commonly associated with hepatitis C virus infection. The negative impact of HCV infection on sexual function is associated with a poor quality of life (QoL) [10]. Sexual dysfunction was observed to be an infrequent side effect of pegylated interferon and ribavirin therapy [11].

The literature suggests that DAA can improve erectile function in patients with HCV [12]. The effect of DAA therapy on sexual function of male HCV infected patients is not well-studied in literature.

Our study aimed to compare the effects of using SOF/daclatasvir and SOF/ledipasvir in the treatment of erectile function induced by chronic HCV infection in Egyptian patients.

PATIENTS AND METHODS

The study protocol was in accordance with the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the ethics committee of our institution. Informed consent was signed by all participants. The patients and controls were recruited from the outpatient clinics of the Tropical Medicine and Dermatology Departments.

A total of 200 treatment-naïve male patients with chronic HCV infection, diagnosed by HCV antibodies and circulating HCV-RNA detected by PCR, and 100 healthy HCV antibody negative, HBV antigen negative, married, sexually active control subjects were included in this study. Patients with clinical or laboratory markers of advanced hepatic disease were excluded. We also excluded patients with organic erectile dysfunction (ED) or other risk factors for ED, such as diabetes mellitus, hypertension, and other causes of hepatitis; patients undergoing pelvic surgery; and patients with renal, malignant, endocrinal, neurological, and hematological disorders. We used the validated Arabic version of the Hospital Anxiety and Depression Scale to exclude subjects with depression [13].

The patients were randomly allocated into groups A and B, treated with SOF 400 mg/ledipasvir 90 mg (Harvoni) and SOF 400 mg/daclatasvir 60 mg, respectively, for 3 months. Guided by PCR findings, the patients were followed up to confirm virologic cure, defined as having undetectable HCV-RNA by PCR COBAS® TaqMan® HCV Test (Roche) in serum.

Thorough history-taking and careful general and genital local clinical examinations were conducted before and after DAA therapy. The validated Arabic version of the International Index of Erectile Function-5 questionnaire (IIEF-5) was administered to all patients before and after completion of therapy and 3 months after cessation of therapy [14]. Baseline IIEF-5 questionnaires were also compared with a similar number of matched healthy control subjects. The IIEF-5 scale assesses the ability to maintain erection, the frequency of maintaining erection, erection confidence, the degree of erection firmness, and overall satisfaction with intercourse, with total scores ranging from 5 to 25. Scores of 22–25 indicate the absence of ED, whereas scores of 5-7, 8-11, 12-16, and 17-21 suggest severe, moderate, mild-moderate, and mild ED, respectively [15].

Fasting venous blood samples were withdrawn from the subjects to evaluate fasting blood sugar, serum albumin, liver function tests, renal function tests, serum bilirubin, serum prolactin, and international normalized ratio (INR). Blood samples were centrifuged at 3000 rpm for 15 min, and the obtained serum was frozen at -80°C until the hormonal assay. Serum total testosterone (TT) and sex hormone-binding globulin (SHBG) levels were evaluated via chemiluminescent immunoassay (Beckman Coulter Inc.©). Free testosterone (FT) serum levels were calculated using the Vermeulen formula [16].

Statistical analysis of the data

Data analyses were performed using the IBM SPSS software package version 20.0. (IBM Corp., Armonk, NY, USA). The Kolmogorov–Smirnov test was used to check the normality of distribution of variables. A Chi-square test (Fisher or Monte Carlo) was used to compare groups of qualitative data. For normal quantitative data, Student's t-test was used to make comparisons between two groups. ANOVA was used to make comparisons between three groups, followed by Tukey's post hoc test for pairwise comparisons. For comparisons between more than two time periods, a repeated measures ANOVA was used,

followed by Bonferroni-adjusted post hoc test for pairwise comparisons. For abnormally distributed quantitative variables, the Friedman test was used. Statistical significance was set at 5%.

RESULTS

Characteristics of the studied groups

Patients had an age range of 30-45 years in group A and 29-47 years in group B. Serum total bilirubin was elevated in most of the patients (68% and 80% in groups A and B, respectively). About 75% of the subjects in both patient groups had normal serum albumin levels. INR was normal in 64% of patients in group A and in more than 50% of patients in group B. Renal function, as assessed by serum creatinine and urea, was normal in nearly all patients. All patients had normal TT levels. FT levels were not significantly different between the two groups. Serum prolactin was also normal in 85% and 90% of the patients in groups A and B, respectively. Sex hormone binding globulin (SHBG) was elevated in all patients in groups A and B (Table 1). Table 1 summarizes the laborato-

Table 1 - Laboratory characteristics of the studied groups.

	Group A (n = 100)	*Group B (n = 100)*	*p*
Age (years) Mean±SD	37.2±4.2	38.2±4.7	0.092[a]
ALT (U/L) Normal (≤41) Elevated (>41)	63 (63%) 37 (37%)	73 (73%) 27 (27%)	0.130[b]
AST (U/L) Normal (≤40) Elevated (>40)	87 (87%) 13 (13%)	77 (77%) 23 (23%)	0.066[b]
Serum total bilirubin (mg/dL) Normal (≤1) Elevated (>1)	32 (32%) 68 (68%)	20 (20%) 80 (80%)	0.053[b]
Serum albumin (mg/dL) Normal (3.5-5.4) Elevated	75 (75%) 25 (25%)	72 (72%) 28 (28%)	0.631[b]
INR Normal (0.8-1.2) Elevated	36 (36%) 64 (64%)	49 (49%) 51 (51%)	0.063[b]
Serum creatinine (mg/dL) Normal (0.7-1.2) Elevated	90 (90%) 10 (10%)	96 (96%) 4 (4%)	0.096[b]
Urea (mg/dL) Normal (10-50) Elevated	98 (98%) 2 (2%)	100 (100%) 0 (0%)	0.497[c]
TT (nmol/L) Normal Diminished (<10.4 nmol/L)	100 (100%) 0 (0%)	100 (100%) 0 (0%)	–
SHBG (nmol/L) Mean±SD	74.93±11.19	72.8±11.33	0.315[a]
FT (nmol/L) Normal Low (<0.1735 nmol/L)	50% 50%	47% 53%	0.32[c]
Serum prolactin (ng/mL) Normal (4.04-15.2) Elevated	85 (85%) 15 (15%)	90 (90%) 10 (10%)	0.285[b]

[a]Student's t-test; [b]Chi-square test; [c]Fisher's Exact test; p: p-value of comparisons between the studied groups
*: Statistically significant (p ≤0.05); Group A: SOF/ledipasvir group Group B: SOF/daclatasvir group.

ry findings of the two studied groups. All subjects were negative for HIV and HBV. The HCV genotype was type 4 (HCV-4) which is the predominant genotype in Egypt. All patients were classified as Child-Pugh stage A-B, with mild degree of fibrosis index and elastography ranged from 8-9.2 KPascale using Fibroscan. The age of the control subjects ranged from 29-47 years. Total testosterone, free testosterone and SHBG were normal in 100% of the control subjects.

Comparison of baseline International index of erectile function-5 (IIEF-5) scores between patients and controls

The prevalence of ED was 74.5% in the patient groups and 14% among controls. About 45% and 33% of the patients in groups A and B, respectively, had mild-moderate ED, whereas 86% of the control subjects reported normal erectile function (p <0.001). The mean IIEF-5 scores of group A, group B, and controls were 17.1±3.4, 18.2±3.4, and 23.7±2.3, respectively (Table 2).

Comparison of International index of erectile function-5 (IIEF-5) scores between patients and controls at the end of treatment

At the end of treatment, mean IIEF-5 score was significantly higher in group B (22.5±2.6) and in controls (23.7±2.3) compared with group A (17.3±3.3) (p<0.001) (Table 3). Group B and controls showed no significant difference in mean IIEF-5 score (p=0.038) (Table 3).

Comparison of International index of erectile function-5 (IIEF-5) scores between patients and controls 3 months after end of therapy

Three months after the end of therapy, there were no significant differences in mean IIEF-5 scores among all groups (group A: 23.1±1.9, group B: 23.3±1.9, controls: 23.7±2.3) (Table 4).

Table 2 - Comparison of IIEF-5 scores before treatment.

Before treatment	*Group A (n = 100)*	*Group B (n = 100)*	*Control (n = 100)*
Severity of ED			
Normal	20 (20%)	31 (31%)	86 (86%)
Mild	31 (31%)	38 (38%)	14 (14%)
Mild-moderate	45 (45%)	31 (31%)	0 (0%)
Moderate	4 (4%)	0 (0%)	0 (0%)
Severe	0 (0%)	0 (0%)	0 (0%)
Total IIEF-5 score			
Mean±SD	17.1±3.4 (19–22)	18.2±3.4 (12–23)	23.7±2.3 (18–25)
F (p)	<0.001* p_1=0.029*, p_2<0.001*, p_3<0.001*		

F: F for ANOVA test; pairwise comparisons between groups were conducted using Tukey's post hoc test; p: p-value of comparisons between the studied groups; p_1: p-value of comparisons between group A and group B; p_2: p-value of comparisons between group A and control; p_3: p-value of comparisons between group B and control; *: Statistically significant (p≤0.05); Group A: SOF/ledipasvir group Group B: SOF/daclatasvir group.

Table 3 - Comparison of IIEF-5 scores at the end of treatment in the three groups.

After treatment	*Group A (n = 100)*	*Group B (n = 100)*	*Control (n = 100)*
Severity of ED			
Normal	20 (20%)	71 (71%)	86 (86%)
Mild	35 (35%)	27 (27%)	14 (14%)
Mild-moderate	41 (41%)	2 (2%)	0 (0%)
Moderate	4 (4%)	0 (0%)	0 (0%)
Severe	0 (0%)	0 (0%)	0 (0%)
Total IIEF-5 score			
Mean±SD	17.3±3.3 (10-22)	22.5±2.6 (15-25)	23.7±2.3 (18-25)
F (p)	<0.001* p_1<0.001*, p_2<0.001*, p_3 0.038*		

F: F for ANOVA test; pairwise comparisons between groups were conducted using Tukey's post hoc test; p: p-value of comparisons between the studied groups; p_1: p-value of comparisons between group A and group B; p_2: p-value of comparisons between group A and control; p_3: p-value of comparisons between group B and control; *: Statistically significant (p≤0.05); Group A: SOF/ledipasvir group Group B: SOF/daclatasvir group.

Comparison of International index of erectile function-5 (IIEF-5) scores before and after treatment in each patient group

Group B had significantly higher post-treatment mean IIEF-5 scores (22.5±2.6) than pre-treatment scores (18.2±3.4). Moreover, the mean IIEF-5 scores 3 months after the end of treatment (23.3±1.9) was significantly higher than the post-treatment score (p <0.001). Group A, however, had no significant differences between posttreatment (17.3±3.3) and pre-treatment (17.1±3.4) mean IIEF-5 scores. However, their mean IIEF-5 score 3 months after the end of therapy were significantly higher than their post-treatment score (p<0.001) (Table 5).

Sex hormone-binding globulin (SHBG), serum total testosterone (TT), and free testosterone (FT) in both patient groups

Compared with the pre-treatment values, SHBG significantly decreased after treatment in groups A (from 74.93±11.19 to 63.4±11.9 nmol/L, p=0.001) and B (from 72.8±11.33 to 66.14±9.8 nmol/L,

Table 4 - Comparison of IIEF-5 scores 3 months after the end of treatment in the three groups.

After 3 months of treatment	*Group A (n = 100)*	*Group B (n = 100)*	*Control (n = 100)*
Severity of ED			
Normal	79 (79%)	86 (86%)	86 (86%)
Mild	21 (21%)	13 (13%)	14 (14%)
Mild–moderate	0 (0%)	1 (1.0%)	0 (0%)
Moderate	0 (0%)	0 (0%)	0 (0%)
Severe	0 (0%)	0 (0%)	0 (0%)
Total IIEF-5 score			
Mean±SD	23.1±1.9 (17-25)	23.3±1.9 (16-25)	23.7±2.3 (18-25)
F(p)	0.220 p_1>0.05, p_2>0.05, p_3>0.05		

F: F for ANOVA test; pairwise comparisons between groups were conducted using Tukey's post hoc test; p: p-value of comparisons between the studied groups; p_1: p-value of comparisons between group A and group B; p_2: p-value of comparisons between group A and control; p_3: p-value of comparisons between group B and control; *: Statistically significant (p≤0.05); Group A: SOF/ledipasvir group Group B: SOF/daclatasvir group.

Table 5 - Comparison of IIEF-5 scores between the three studied groups during different treatment periods.

	Group A (n = 100)			*Group B (n = 100)*			*Control (n = 100)*
	Before treatment	*After treatment*	*After 3 months*	*Before treatment*	*After treatment*	*After 3 months*	
Severity of ED							
Normal	20 (20%)	20 (20%)	79 (79%)	31 (31%)	71 (71%)	86 (86%)	86 (86%)
Mild	31 (31%)	35 (35%)	21 (21%)	38 (38%)	27 (27%)	13 (13%)	14 (14%)
Mild-moderate	45 (45%)	41 (41%)	0 (0%)	31 (31%)	2 (2%)	1 (1.0%)	0 (0%)
Moderate	4 (4%)	4 (4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Severe	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Fr (p)	*<0.001**			*<0.001**			
χ^2p	p<0.001*[a]	p<0.001*[a]	p=0.300[b]	p<0.001*[a]	p=0.128[a]	p=1.000[b]	
Total IIEF-5 score Mean±SD	17.1±3.4 (9-22)	17.3±3.3 (10-22)	23.1±1.9 (17-25)	18.2±3.4 (12-23)	22.5±2.6 (15-25)	23.3±1.9 (16-25)	23.7±2.3 (18-25)
F (p)							
Significance at different periods	p_1=0.284, p_2<0.001*, p_3<0.001*			p_1<0.001*, p_2<0.001*, p_3<0.001*			
tp	<0.001*	<0.001*	0.092	<0.001*	<0.001*	0.235	

Fr: Friedman test; b: Chi-square test; a: Monte Carlo; F: F test (ANOVA) with repeated measures; statistical significance between periods was assessed using Bonferroni-adjusted post hoc test; p: p-value of comparisons between the different periods; p_1: p-value of comparisons between before and after treatment; p_2: p-value of comparisons between before and after 3 months of treatment; p_3: p-value of comparisons between after and after 3 months of treatment; χ_2p: p-value of comparing controls and all other groups; tp: p-value of Student's t-test for comparing controls and all other groups; *: Statistically significant (p≤0.05); Group A: SOF/ledipasvir group Group B: SOF/daclatasvir group.

p=0.0002). TT levels significantly decreased after treatment in groups A (from 16.075±1.94 to 12.53±1.63 nmol/L, p=0.003) and B (from 16.51±2.47 to 12.68±1.9 nmol/L, p=0.01). In groups A and B, the FT levels at the end of treatment (0.17±0.05 and 0.18±0.04 nmol/L) were not significantly different compared with the pre-treatment values (0.16±0.05 and 0.17±0.04 nmol/L) (p=0.50 and p=0.417). However, the percentage of patients with low FT was significantly higher in group A than in group B (p=0.006).
The SHBG levels 3 months after cessation of therapy were significantly lower than the pre-treatment values in groups A (48.2±3.6 nmol/L) and B (48.4±4.5 nmol/L) (p<0.001). In groups A and B, the FT levels were significantly higher (0.19±0.06 and 0.18±0.05 nmol/L) compared with the pre-treatment values (0.16±0.05 and 0.17±0.04 nmol/L) (p=0.04 and p=0.02). The percentage of patients with low FT was not significantly different between groups A and B (p=0.09).

Relation of International index of erectile function-5 (IIEF-5) scores to age in the patient groups before and after treatment

There was no significant relationship between age and IIEF-5 score before and after treatment in groups A (p=0.178 and p=0.114) and B (p=0.901 and p=0.985).

DISCUSSION

Sexual dysfunction is commonly encountered in the setting of HCV infection. Chronic HCV infection is known to affect male sexual function even before the development of cirrhosis. This may be explained by the fact that the nonstructural proteins of HCV induce a state of systemic inflammation and subsequent oxidative stress in the penile endothelium. Furthermore, psychological factors or the associated extrahepatic diseases may also contribute to pre-cirrhotic male sexual function impairment [12].
Progression to cirrhosis is associated with increased serum estradiol levels and a lower total plasma testosterone due to reduced production by atrophic testes with increased estrogen: testosterone ratios [28]. Additionally, the SHBG level is elevated, which decreases the amount of biologically active circulating peripheral androgens. Portal hypertension further can lead to hyperestrogenism, resulting in feminization as well as suppression of hypothalamic/pituitary secretion of GnRH/ gonadotropins. Cirrhosis is also associated with elevated prolactin levels that suppress hypothalamic and pituitary production of GnRH/ gonadotropins [17]. It was also observed that sexual dysfunction was reported in patients following pegylated interferon and ribavirin therapy. It was suggested that interferon may have a direct impact on the gonads decreasing testosterone production or an indirect psychological influence inducing the partial impairment of sexual desire and satisfaction [11].
Modern therapy with DAAs is associated with high SVR rates [18]. It has been reported that patients achieving SVR-12 experience improvement of sexual function and satisfaction. The reduction of SHBG and increased bioavailable testosterone (BioT) in patients with HCV achieving SVR-12 after the DAA therapy enhances the androgenic action which is detrimental for male sexual function [19].
Our patients with chronic HCV infection had lower IIEF-5 scores compared with healthy controls. This supports the fact that HCV infection can negatively impact erectile function. A study has reported a similarly high prevalence of sexual dysfunction in patients with chronic HCV compared with healthy controls and attributed these to multiple factors, including depressive symptoms and antidepressant use [20].
It was previously proposed that IFN-RBV therapy associated with sexual impairment could be secondary to depression, decreased testicular testosterone production, or viral effects on the pathophysiologic mechanism of erection [11]. Recent studies have suggested that therapy with new DAAs is associated with improvement of male sexual function [12, 21]. However, it has also been reported that sexual dysfunction could be an unrecognized side effect of SOF/ledipasvir [22].
Improvement of erectile function has been reported in patients after 12 weeks of DAA therapy [12]. Another study observed significant improvements in erectile function, orgasm, desire, intercourse, and overall satisfaction as reported by patients receiving SOF 400 mg, daclatasvir 60 mg, and RBV 200 mg [21]. The pathogenesis of sexual dysfunction in male patients with HCV can be caused by a combination of several factors, including hormonal changes, psychological factors, and

medications [23]. A decline in serum testosterone has been reported in patients with early hepatic cirrhosis; however, this is reversed in advanced cirrhosis [24, 25]. An increased serum level of prolactin has also been associated [26]. Serum SHBG elevation and subsequent bioactive testosterone reduction in patients with HCV have been reported. SHBG has a high affinity with and binds to testosterone, thereby affecting the amount of active testosterone available in target tissues [27]. Moreover, about 80% of circulating testosterone is bound to SHBG. Therefore, serum SHBG level is inversely related to bioavailable testosterone [28]. SHBG is elevated in patients with hepatitis, which correlates with liver condition [29]. It has been proposed that the SHBG level will decrease upon the restoration of liver function after DAA therapy, thus increasing testosterone bioavailability and thereby improving sexual function [21].

We reported that TT and SHBG significantly decreased at the end of treatment in both treatment groups. This likely reflects the decline in SHBG with HCV clearance. TT levels in HCV are considered to be a reflection of SHBG levels, with higher SHBG leading to higher serum TT levels, regardless of true gonadal status [30].

We observed that treatment with SOF+DAC was associated with better erectile function compared to SOF/LDP at the end of treatment. Erectile function in patients receiving SOF+DAC was not different from healthy controls at the end of therapy. This could be because patients in the SOF/LDP treatment group had a higher percentage of normal FT at end of treatment compared with patients in the SOF/LDP treatment group.

Erectile function in both treatment groups improved at 3 months after cessation of treatment compared with that at the end of treatment. This could be a result of the observed significant increase in FT levels in both treatment groups. This increase in FT levels following HCV clearance is most likely due to the improvement of hepatic testosterone metabolism following recovery [30].

Age reportedly had a negative impact on IIEF-5 scores in patients receiving DAA [12]. However, we reported no relation between IIEF-5 scores and age after treatment. This might be due to the relatively younger patient population recruited in our study.

Erectile function significantly improved at the end of treatment in patients receiving SOF+DAC. This contrasts with patients receiving SOF/LDP, who had no significant improvement. Erectile function in both treatment groups was not significantly different from healthy controls 3 months after the end of therapy. We suggest that SOF+DAC is associated with the earlier improvement of erectile function compared with SOF/LDP. However, this study is limited because it recruited patients suffering from mild cirrhotic changes or no cirrhosis only. In conclusion, SOF+DAC may be preferred over SOF/LDP in patients with chronic HCV with ED or with predisposing factors for ED.

Conflict of interests
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REFERENCES

[1] Gower E, Estes C, Blach S, Razavi-Shearer K, Razavi H. Global epidemiology and genotype distribution of the hepatitis C virus infection. *J Hepatol*. 2014; 61 (1 Suppl.), S45-57.

[2] EL-Ghitany EM. Hepatitis C virus infection in Egypt: Current situation and future perspective. *JHIPH*. 2019; 49 (1), 1-9.

[3] Alexopoulou A, Karayiannis P. Interferon-based combination treatment for chronic hepatitis C in the era of direct acting antivirals. *Ann Gastroenterol*. 2015; 28 (1), 55-65.

[4] Holmes JA, Thompson AJ. Interferon-free combination therapies for the treatment of hepatitis C: current insights. *Hepat Med*. 2015; 7, 51-70.

[5] Sabal AA, Omar HM, El-Taher SM, El-Deen NM, El Kassas M. Efficacy of 24-week treatment with sofosbuvir/daclatasvir/ribavirin in chronic hepatitis C virus-infected Egyptian patients with previous sofosbuvir-based treatment failure. *Sci J Al-Azhar Med Fac Girls*. 2020; 4, 474-81.

[6] Ahmed OA, Kaisar HH, Badawi R, et al. Efficacy and safety of sofosbuvir-ledipasvir for treatment of a cohort of Egyptian patients with chronic hepatitis C genotype 4 infection. *Infect Drug Resist*. 2018; 11, 295-8.

[7] Backus LI, Belperio PS, Shahoumian TA, Mole LA. Direct-acting antiviral sustained virologic response: Impact on mortality in patients without advanced liver disease. *Hepatology*. 2018; 68 (3), 827-38.

[8] Omar H, El Akel W, Elbaz T, et al. Generic daclatasvir plus sofosbuvir, with or without ribavirin, in treatment of chronic hepatitis C: real-world results from 18 378 patients in Egypt. *Aliment Pharmacol Ther*. 2018; 47 (3), 421-31.

[9] El-Khayat HR, Kamal EM, El-Sayed MH, et al. The effectiveness and safety of ledipasvir plus sofosbuvir in adolescents with chronic hepatitis C virus genotype 4 infection: a real-world experience. *Aliment Pharmacol Ther*. 2018; 47 (6), 838-44.
[10] Marino Z, Rodriguez-Tajes S, Bartres C, et al. Improvement of sexuality after hepatitis C cure with direct acting antivirals. *Liver Int*. 2020; 40 (12), 2972-7.
[11] Fawzy N, Atia HA, Galal SM, Shawky JA. Prevalence and risk factors of erectile dysfunction among chronic hepatitis C male patients treated with pegylated interferon-α and ribavirin. *Egypt J Psychiatr*. 2015; 36, 40-4.
[12] Elshimi E, Morad W, Mohamad NE. Male Sexual Dysfunction Among Egyptian Patients with Chronic Hepatitis C Virus Infection Before and After Direct-Acting Antiviral Drugs. *J Sex Med*. 2019; 16 (3), 402-9.
[13] Terkawi AS, Tsang S, AlKahtani GJ, et al. Development and validation of Arabic version of the Hospital Anxiety and Depression Scale. *Saudi J Anaesth*. 2017; 11 (Suppl. 1), S11-S8.
[14] Shamloul R, Ghanem H, Abou-zeid A. Validity of the Arabic version of the sexual health inventory for men among Egyptians. *Int J Impot Res*. 2004; 16 (5), 452-5.
[15] Rhoden EL, Teloken C, Sogari PR, Vargas Souto CA. The use of the simplified International Index of Erectile Function (IIEF-5) as a diagnostic tool to study the prevalence of erectile dysfunction. *Int J Impot Res*. 2002; 14 (4), 245-50.
[16] Ho CK, Stoddart M, Walton M, Anderson RA, Beckett GJ. Calculated free testosterone in men: comparison of four equations and with free androgen index. *Ann Clin Biochem*. 2006; 43 (Pt 5), 389-97.
[17] Neong SF, Billington EO, Congly SE. Sexual dysfunction and sex hormone abnormalities in patients with cirrhosis: review of pathogenesis and management. *Hepatology*. 2019; 69 (6), 2683-95.
[18] Wu PS, Chang TS, Lu SN, et al. An investigation of the side effects, patient feedback, and physiological changes associated with direct-acting antiviral therapy for hepatitis C. *Int J Environ Res Public Health.* 2019; 16 (24).
[19] Huang YP, Liu W, Chen SF, et al. Free testosterone correlated with erectile dysfunction severity among young men with normal total testosterone. *Int J Impot Res*. 2019; 31 (2), 132-8.
[20] Fabregas BC, Moura AS, Avila RE, et al. Sexual dysfunction and dissatisfaction in chronic hepatitis C patients. *Rev Soc Bras Med Trop.* 2014; 47 (5), 564-72.
[21] Akl EM, Salah AA. Effect of new oral direct acting antiviral therapy on sexual function in male patients with hepatitis C virus. *Andrologia*. 2020; e13835.
[22] Lenz DU, Crutcher EL, Greene EM. Sexual dysfunction in a patient taking ledipasvir/sofosbuvir for the treatment of hepatitis C: a case report. *J Pharm Pract*. 2019; 32 (2), 231-5.
[23] Fusco F, D'Anzeo G, Rossi A, et al. Erectile dysfunction in patients with chronic viral hepatitis: a systematic review of the literature. *Expert Opin Pharmacother*. 2013; 14 (18), 2533-44.
[24] Himoto T, Fujita K, Sakamoto T, et al. Clinical efficacy of free androgen index, a surrogate hallmark of circulating free testosterone level, in male patients with HCV-related chronic liver disease. *J Clin Biochem Nutr*. 2018; 63 (3), 238-45.
[25] El-Serafi AT, Osama S, El-Zalat H, IM EL-D. Dysregulation of male sex hormones in chronic hepatitis C patients. *Andrologia*. 2016; 48 (1), 82-6.
[26] Hofny ER, Ali ME, Taha EA, et al. Semen and hormonal parameters in men with chronic hepatitis C infection. *Fertil Steril*. 2011; 95 (8), 2557-9.
[27] Liu C-H, Huang Y-J, Yang S-S, et al. Generic sofosbuvir-based interferon-free direct acting antiviral agents for patients with chronic hepatitis C virus infection: a real-world multicenter observational study. *Sci Rep*. 2018; 8 (1), 13699.
[28] Hammond GL. Plasma steroid-binding proteins: primary gatekeepers of steroid hormone action. *J Endocrinol.* 2016; 230 (1), R13-25.
[29] Thaler MA, Seifert-Klauss V, Luppa PB. The biomarker sex hormone-binding globulin - from established applications to emerging trends in clinical medicine. *Best Pract Res Clin Endocrinol Metab.* 2015; 29 (5), 749-60.
[30] Chaudhury CS, Mee T, Chairez C, et al. Testosterone in men with chronic hepatitis c infection and after hepatitis C viral clearance. *Clin Infect Dis*. 2019; 69 (4), 571-6.